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Preparation of tetrazole derivatives in new crystal form

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Ljubljana, 19 January 2005

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REQUEST FOR A PATENT GRANT	
1. Address for correspondence: LEK Pharmaceuticals d.d. Intellectual Property Department Verovškova 57, SI – 1526 Ljubljana, Slovenia Telephone: 580 20 05 Fax: 568 2123 code: pš/33140/SI/PSK	Acknowledgement of the application <i>(for official use only)</i> Date of application receipt: 5 November 2003 Application number: P-200300270 Stamp and signature:
2. Applicant (Family name followed by given name and address; for a legal entity, full official designation) Lek Pharmaceuticals d.d. Verovškova 57 SI - 1526 Ljubljana Slovenia	
3. Representative:	Registration No.:
4. Inventor (Family name followed by given name and address): Ljubo Antončič, Podmiljščakova 43, SI-1000 Ljubljana	
5. Title of invention: Preparation of tetrazole derivatives in a new crystal form	
6. Claimed priority right:	
7. Additional requests: <input type="checkbox"/> application for a shortened duration patent <input type="checkbox"/> preliminary publication after the expiry of ____ months <input type="checkbox"/> application is divided from the application no.: ____	
8. Statements: <input type="checkbox"/> statement of common representative	

9. Enclosures:

- x Description of the invention, having 10 pages
- x Patent claim (claims), having 2 pages; number of claims: 11
- x Schemes (if required for patent description); number of sheets: 4
- x Abstract
- ☐ Voucher for the settlement of fees
- ☐ Declaration of depositing the biological material if it is an invention which cannot be described
- ☐ Authorisation to the representative
- ☐ General authorisation to the representative is deposited in the office under no.
- ☐ Declaration on priority right
- ☐ Information about additional applicants
- x Information about additional inventors
- ☐ Presentation of nucleotide or amino acid sequence in the description
- ☐ Application was previously faxed or mailed in electronic form
- ☐ _____

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Our Ref: pš/33140/SI/PSK Your Ref:

Annex to the request for a patent grant

Information about additional inventors:
Preparation of tetrazole derivatives in a new crystal form

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Preparation of tetrazole derivatives in a new crystal form

Field of the invention

(IPC⁷ C 07 D 403/10, A 61 K 9/19)

The present invention belongs to the field of chemistry of heterocyclic compounds and pharmaceutical industry and relates to a novel crystal form of a pharmaceutically useful crystalline potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole and the new mode of its preparation.

Technical problem

2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole is the pharmaceutical substance acting on the last step of the cascade renin-angiotensin system by binding to the angiotensin II receptor. By utilizing said biochemical effect losartan is generally used as an effective antihypertensive agent in the form of a potassium salt. In pharmaceutical compositions it is often combined with diuretics.

There is a need for pharmaceutical active substances of high purity in such a form to be simply incorporated into a pharmaceutical formulation which provides high bioavailability. For incorporation into a pharmaceutical formulation, pharmaceutical active substances must have defined desired physicochemical properties and in addition to high purity, suitable stability, nonhygroscopicity, appropriate solubility and compatibility with the excipients are demanded. The above may be achieved with a choice of the adequate isomer, for example, only one optical isomer, a choice of the adequate polymorph or even with a choice of the particles of the adequate form and size range the most suitable for incorporation into a pharmaceutical formulation.

Prior art

The substituted imidazoles with an action on the renin-angioten system of the blood pressure regulation are in the patent EP 253310 and US Pat. No. 5,138,069.

It is known that 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole and potassium salt thereof, respectively, exists in several polymorphic forms [K. Raghavan et al., Pharm. Res., 1993, 103 900-904; L. S. Wu et al., Pharm. Res., 1993, 10, 1793-1795]. The authors of US Pat. No. 5,608,075 present that polymorphic form I, characterized by DSC endotherm at 229.5°C, while heating transforms to polymorphic form II characterized with the endothermic peak of melting at 273.2°C. Form I is stable at room temperature, Form II is stable at higher temperatures. Therefore, Form II gradually converts to thermodynamically more stable Form I under normal conditions of handling.

SI 200300145 describes a potassium salt of substituted imidazole in a polymorphic form with the bound water (water content 7 to 12 weight percent) named Form III. The patent discloses that Form III was isolated in the form with three bound molecules of water *per* molecule of the active substance, and at heating the polymorphic form with two bound molecules of water *per* molecule of the active substance was also formed. Physical analysis of that form has shown that it is a polymorphic form in the form of dihydrate thus with two crystal-bound molecules of water *per* molecule of the active substance. The authors of the patent WO 03048135 succeeded in preparing a similar substance – a polymorphic form with the bound water between 12% and 16% (wt. %). Said patent also discloses further two polymorphic forms of potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole characterized by peak diffractions on the powder diffraction pattern at about 4.3, 15.6 and 23.4 degrees 2θ named Form IV, and another polymorphic form named Form V characterized by peak diffractions on the powder diffraction pattern at about 6.4, 12.2, 20.7, 21.5 and 22.5 degrees 2θ.

Likewise, SI 200300025 discloses the preparation of alkali or alkali-earth salts of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole in the form of a fine amorphous powder by lyophilization of an aqueous solution of alkali or alkali-earth salt of said substituted imidazole, or the same by evaporation according to SI 200200145.

It is known that a defined form of a polymorph itself does not provide demanded suitable physicochemical properties. In US Pat. No. 5,859,258 losartan of polymorphic form I was crystallized from a mixture of *i*-propanol and 2.4–2.6% of water. It has been found that uncontrolled crystallization may result in formation of large three-dimensional complexes which are inappropriate for incorporation into a pharmaceutical formulation, and the patent discloses the very rigorously controlled process demanding fulfilment of 14 different conditions in order to obtain the desired morphology of the particles for pharmaceutical use.

From the prior art it is evident that an essential element for the preparation of crystal forms of said active substance with the bound water is the presence of water in a combination with a suitable solvent or the presence of water in the form of atmospheric humidity. The crystal form with about 7 to about 12% water was isolated from a combination of solvents and water or by exposing of the amorphous substance to atmospheric humidity, and the crystal form with from 12 to 16% water was prepared only by exposure of amorphous losartan potassium or by relatively long exposure of losartan potassium of form I to controlled atmospheric humidity above 80% relative humidity.

Unlike US Pat. No. 5859258 where a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole of form I was crystallized from a combination of alcohol and water and according to WO 03048135 preparation of polymorphic form Form IV can be prepared by dissolving losartan potassium in a solvent with a melting point below 135°C and the addition of dichloromethane whereupon the suspension is formed, and polymorphic form Form V by dissolving losartan potassium in a solvent with a melting point below 135°C and the addition of hexane. For both processes the

patent lists alcohols having from 1 to 6 carbon atoms as the most preferred solvents, and in the examples only ethanol is set forth.

Description of the figures

Figure 1: X-ray powder diffractogram of polymorphic form Y of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole

Figure 2: Particle size distribution of the batch LST-K-1434/1 of Example 3

Figure 3: Particle size distribution of the batch LST-K-1434/3 of Example 3

Figure 4: X-ray powder diffractogram of the batch L-3391/A

Description of the invention

The object of the present invention is a completely novel crystal form of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole.

The process disclosed in WO 03048135 describes the formation of Form V with peak diffractions on the X-ray powder diffractogram at about 6.4, 12.2, 20.7, 21.5 and 22.5 degrees 2 θ , from the solvent system comprising one of C₁ – C₆ alcohols and hexane.

From the solvent system methanol – hexane, a polymorphic form with peak diffractions in the X-ray powder diffractogram at about 6.9, 13.8, 20.6, 24.0, 24.8, 28.7 and 29.2 degrees 2 θ can be prepared if a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole of polymorphic form I is dissolved in methanol and the resulting solution is concentrated, while stirring poured into hexane, and the resulting precipitate is filtered and dried.

If a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole is dissolved in methanol to afford a clear solution, said solution is evaporated to a resinous residue which is still clear

and while stirring at room temperature hexane in the several-fold volume overage relative to methanol is added and further stirred at room temperature, upon isolation a new polymorphic form is obtained characterized with peaks on X-ray powder diffractogram at about 6.7, 13.8, 17.4, 19.2, 24.5, 24.8, 25.2 in 28.9 degrees 2 θ .

An identical form is obtained if a clear methanolic solution of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole while stirring at room temperature hexane in the several-fold volume overage relative to methanol is added, seeded with several crystals of polymorph Y and isolated.

A novel polymorphic form of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole characterized with peak diffractions on the X-ray powder diffractogram at about 6.7, 13.8, 17.4, 19.2, 24.5, 24.8, 25.2 in 28.9 degrees 2 θ was named polymorphic form Y. In respect to the mode of isolation its solvates are also the object of the invention.

Polymorphic form Y may be converted to a polymorphic form with peak diffractions on the X-ray powder diffractogram at about 6.9, 13.8, 20.6, 24.0, 24.8, 28.7 and 29.2 degrees 2 θ by drying polymorphic form Y in *vacuo* or under the normal pressure at room temperature or elevated temperature.

Pharmaceutical compositions comprising polymorphic form Y of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole and solvates thereof are also an object of the present invention. The appropriate daily dose contains 1 to 500 mg of polymorphic form Y of potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole and may also contain the other suitable active substances, for example, a diuretic.

A pharmaceutical composition may be in a dosage form suitable for oral or parenteral administration and is indicated for the treatment of hypertension, the pharmaceutical composition, the object of said invention, can be in the form of tablets, capsules, pellets, granules and suppositories. Solid pharmaceutical dosage forms can be coated, for example, with the aim to improve pelletability, or to adjust disintegration and absorption, respectively.

According to the object of the present invention, the film coated tablets may be prepared by the direct dry blend procedure or by the wet granulation method or any other suitable procedure known in pharmaceutical technology.

Experimental part

Powder X-ray diffraction (PXRD) analysis

An apparatus Philips PW1710 with the reflexion technique under the conditions: CuK α radiation, range from 2° to 37° 2 θ with a 0.04y 2 θ step, integration time 1 second was used.

The typical diffractogram of polymorphic form Y of potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole is shown in Figure 1.

Particle size determination

The particles size of the sample was determined on an instrument Malvern Mastersizer S. The sample and 100 mg of DSSS (dioxysulfosuccinate sodium salt) were added to hexane and the suspension was stirred at 2500 rpm. The stabilized suspension was placed into a measuring cell of the instrument and by scattering the monochromatic light on the particles, distribution of the particle size was determined. For calculation Mie's theory of scattering was used, which is universal and as such does not set forth the limitation for measured particle sizes.

Measurement of bulk / tapped volume

In conformity with the technique according to PhEur4, 2.9.15 APPARENT VOLUME and USP 26, <616> BULK DENSITY AND TAPPED DENSITY, 30 g of the substance (m_0) was shaken carefully without compressing in a dry measuring cylinder and the volume V_0 was read on the measuring cylinder scale. Flow density is the quotient of V_0/m_0 (expressed in ml/g), bulk density is the quotient of m_0/V_0 (expressed in g/ml). After the flow density was read, the measuring cylinder was fixed in the apparatus for tapped volume determination. The sample was tapped to the constant volume (1250 taps) and the final volume (V_1) was read. Tapped volume is the quotient of V_1/m_0 (expressed in ml/g), tapped density is the quotient of m_0/V_1 (expressed in g/ml).

Example 1

(Preparation of polymorphic form Y)

10 g of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole was dissolved in 200 ml of methanol. The clear solution was evaporated to a dense but still clear residue just before it began crystallizing (to the weight of ca. 13 g) to which 1000 ml of *n*-hexane was added while stirring at room temperature. It was stirred at room temperature for further 2 hours and filtered. Yield 9.7 g

Example 2

(Alternative mode of the preparation of polymorphic form Y)

10 g of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole was dissolved in 12.5 ml of methanol. The clear solution while stirring was added into 500 ml of *n*-hexane, which had been previously seeded with several crystal of a potassium salt of polymorphic form Y. It was carefully stirred at room temperature and filtered.

Yield 7.9 g. The batch with the code L-3391/A was prepared in similarly described examples.

Example 3

20 g of purified 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole was suspended in 200 ml of water. At room temperature pH was adjusted to 9.3 with a 10% aqueous potassium hydroxide solution. The reaction mixture clarified. The solution was filtered and lyophilized to yield 19.74 g of a white, completely amorphous product. The example was repeated with different amounts of water so that additional 20% and 30% solutions were lyophilized and the batches LST-K-1434/1 (10% solution), LST-K-1434/2 (20% solution) and LST-K-1434/3 (30% solution) were obtained.

Example 4

(Preparation of polymorphic form X)

1 g of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole of form I was dissolved in 20 ml of methanol. The resulting solution was concentrated to a dense, glassy mass and while stirring at room temperature it was poured into 100 ml of *n*-hexane. The resulting precipitate was stirred at room temperature for 1 hour, filtered and dried. Yield 0.92 g. The batch was coded as LST-K-3279. Analogously, the batch LST-K-1481 was prepared, which was additionally ground on a mill Alpine MFC at 5000 rpm and a 0.5 mm screen and the milled batch was coded LST-K-1496/1.

Example 5

(Determination of the particle size and specific surface area)

The particle size was determined by the method of scattering of the laser light – Malvern. The results clearly indicated that the smallest particles were in the sample LST-K-1434/1, and the largest in LST-K-1434/3. The specific surface area was indirectly proportional to the particle size: the largest in the sample of the

batch LST-K-1434/1 and the smallest in the sample of the batch LST-K-1434/3. In addition to the particle size, the solubility parameters were determined for the samples LST-K-1481 and LST-K-1496/2.

Table 1: Particle size and specific surface area

		LST-K-1434/1	LST-K-1434/2	LST-K-1434/3
PARTICLE SIZE	d 0.1 (μm)	5.2	5.6	10
	d 0.5 (μm)	36	63	144
	d 0.9 (μm)	152	322	484
	D[4.3]	61	120	202
	Assessment of specific surface area (m ² /g)	1.1	1.1	1.0
SPECIFIC SURFACE AREA	BET isotherm Calculated external surface (including pores) (m ² /g)	1.27	0.77	0.48

Table 2: Particle size and solubility parameters in comparison with commercially available sample of polymorphic form I of potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole

		LST-K-1481	LST-K-1496/1	Form I	Milled sample of Form I
PARTICLE SIZE	d 0.1 (μm)	8,3	1,1	20	3,3
	d 0.5 (μm)	96	25	86	34
	d 0.9 (μm)	215	58	218	86
	D[4.3]	107	28	105	41
SOLUBILITY (mg/ml)	in water	633		630	
	in 0.1 M HCl	1.74		1.52	
	in glycerol	2.83			
DISSOLUTION RATE (min)	75 mg in 50 ml of 0.1 M HCl	14	13	16	8

Example 6

(Determination of bulk and tapped density and flowability properties)

Table 3 presents bulk and tapped volumes / densities of the samples prepared in Example 3. The batch LST-K-1434/3, also having the largest particles, is the most suitable for pharmaceutical use.

Table 3: Flow and tapped density (volumes)

	LST-K-1434/1	LST-K-1434/2	LST-K-1434/3
Bulk density (g/ml)	0.21	0.32	0.43
Tapped density (g/ml)	0.27	0.41	0.52
Flow density (ml/g)	4.69	3.16	2.32
Tapped volume (ml/g)	3.70	2.45	1.91
Carr index	21.0	22.6	17.8
Hausner index	1.27	1.29	1.22

Example 7

(Stability of the sample from Example 4)

The sample coded LST-K-3279 did not change its polymorphic forms after 45-day storage in the closed plastic flask at room temperature. The sample was exposed to temperatures 60°C and 80°C and negative pressure ~10 mBar. The crystal structure did not change under any of the conditions. Exposed to the above conditions, the sample lost 0.79% (60°C) and 0.90% (80°C) of its weight.

Experiment 8

(Temperature stability of the sample of polymorphic form Y)

10 g of polymorphic form Y of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole was dried. Polymorphic form X was obtained. Yield 9.1g

Claims

1. Polymorphic form Y of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole characterized in that it exist in a crystal form and its X-ray powder diffractogram has diffractions at about 6.7, 13.8, 17.4, 19.2, 24.5, 24.8, 25.2 and 28.9 degrees 2 θ .
2. Polymorphic form Y of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole according to claim 1 characterized in that it has the X-ray powder diffractogram as shown in Figure 1.
3. Polymorphic form Y of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole according to claim 1 characterized in that it exists in a crystal form in a form of the solvate.
4. Polymorphic form of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole selected between a polymorphic form with the diffractions on the X-ray powder diffractogram at about 6.7, 13.8, 17.4, 19.2, 24.5, 24.8, 25.2 and 28.9 degrees 2 θ , or at about 6.9, 13.8, 20.6, 24.0, 24.8, 28.7 and 29.2 degrees 2 θ characterized in that it contains more than 50% of particles having the diameter between about 5 μ m and about 500 μ m.
5. Polymorphic form according to claim 4 characterized in that it contains at least 50% of particles having the diameter below about 100 μ m.
6. The process for the preparation of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole and the solvates thereof characterized by isolation from the mixture of methanol and hexane wherein hexane is in the volume overage to methanol.
7. The process according to claim 6 characterized in that it comprises the following steps:

- a) preparation of a clear methanolic solution of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole,
 - b) optionally concentrating the resulting solution,
 - c) mixing optionally the obtained concentrated solution with the volume overage of hexane to methanol,
 - d) isolation of polymorphic form Y of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole.
8. The process of conversion of polymorphic form Y of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole according to any of claims 1 to 3 to a polymorphic form with the diffractions on the X-ray powder diffractogram at about 6.9, 13.8, 20.6, 24.0, 24.8, 28.7 and 29.2 degrees 2 θ characterized in that polymorphic form Y is dried *in vacuo* or under normal pressure at room temperature or at elevated temperature.
9. The pharmaceutical composition containing as the active substance polymorphic form Y of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole or the solvates thereof.
10. The use of polymorphic form Y of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole for the preparation of a medicament.
11. The use of polymorphic form Y of a potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole according to claim 9 for the preparation of a medicament for the treatment of hypertension.

Preparation of tetrazole derivatives in a new crystal form

Abstract

The new crystal form of a pharmaceutically useful crystalline salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole characterized by peak diffractions on the X-ray powder diffractogram at about 6.7, 13.8, 17.4, 19.2, 24.5, 24.8, 25.2 and 28.9 degrees 2 θ was prepared from the known polymorphic forms from the combination of solvents comprising methanol.

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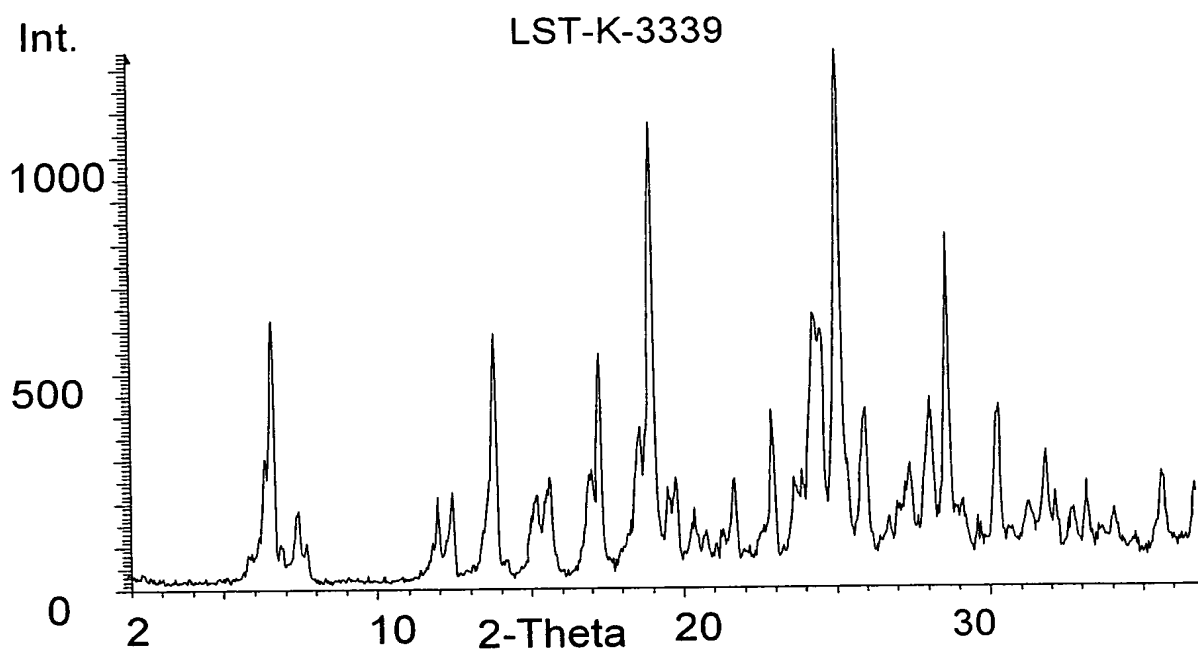


Figure 1

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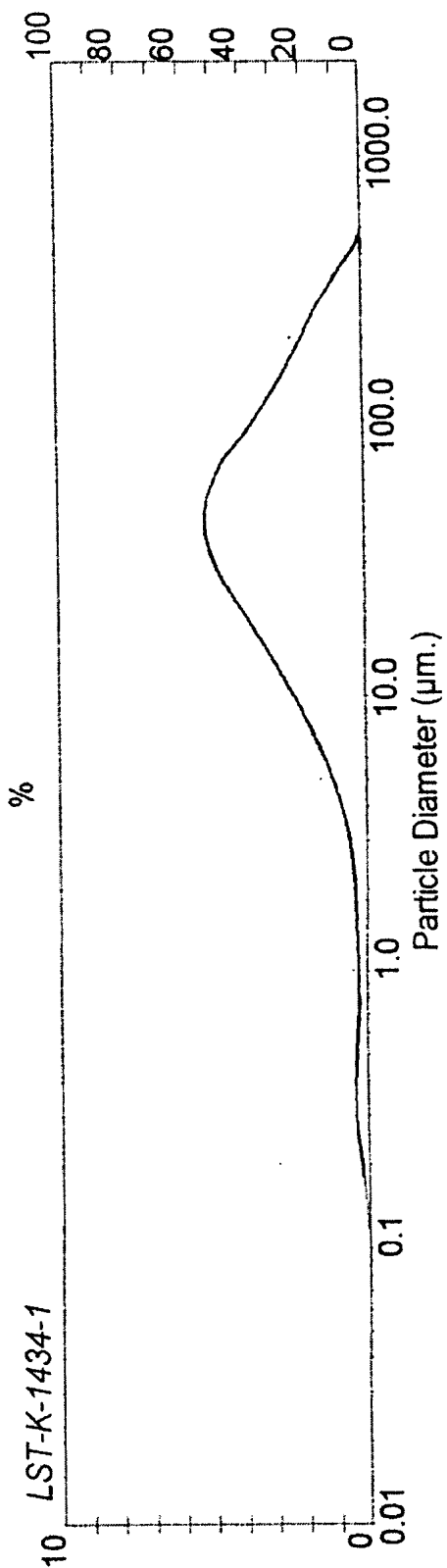


Figure 2

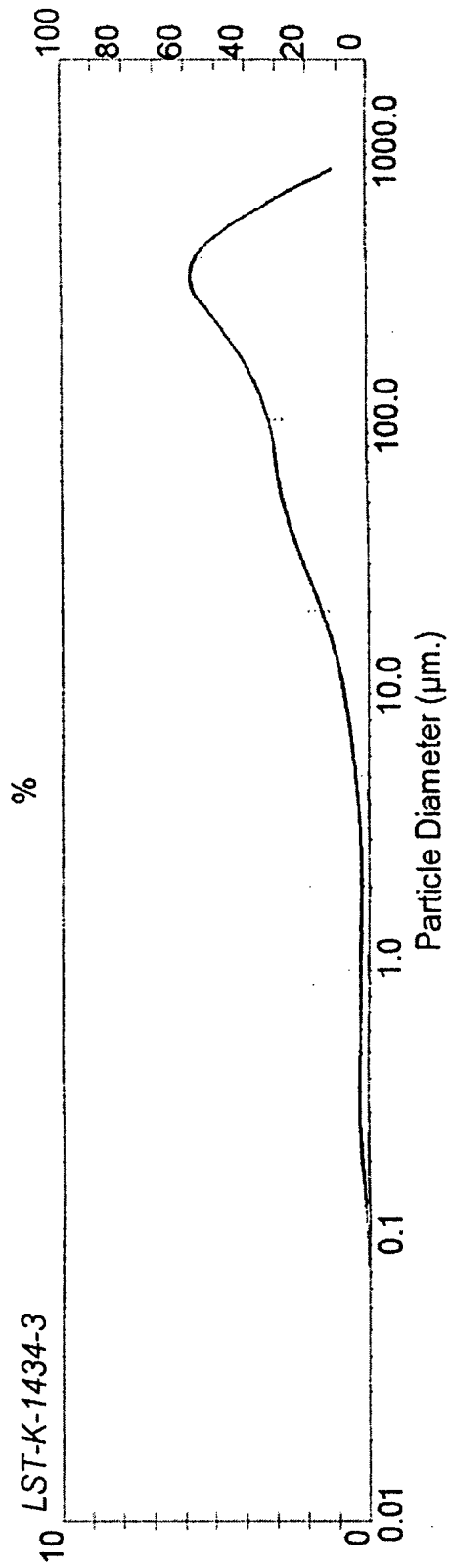


Figure 3

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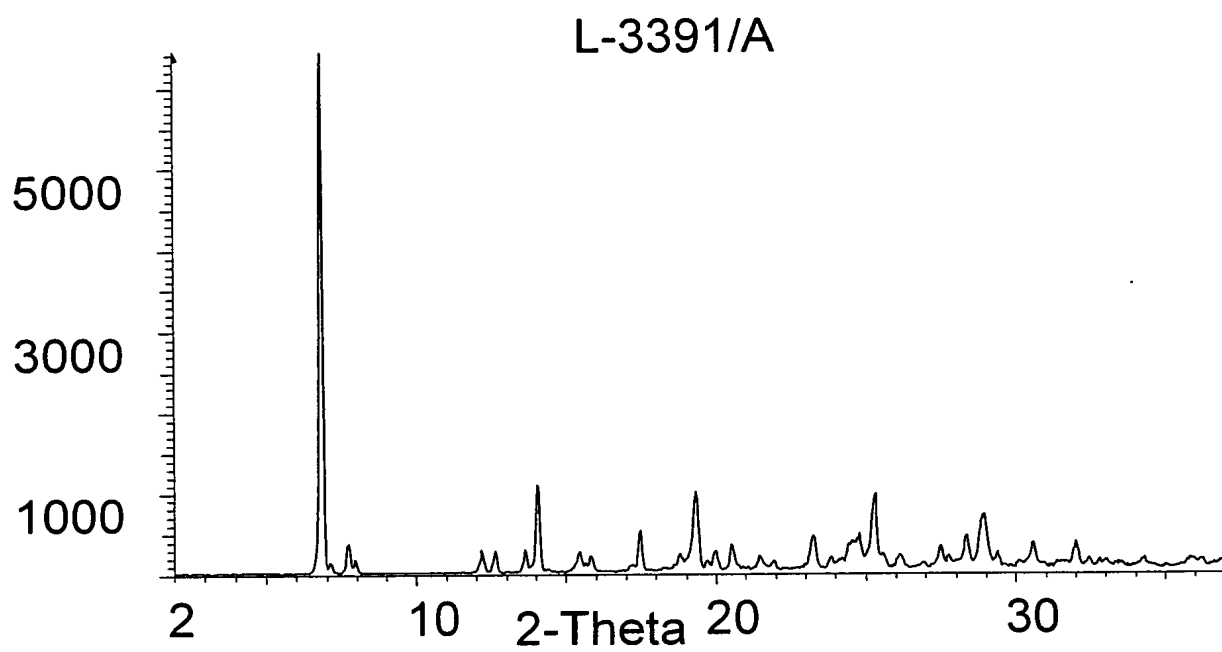


Figure 4

The undersigned Djurdjica Mandrino, permanent court interpreter for the English language, appointed by Decree No. 756-4/91, issued on 11th of February 1991 by the Ministry of Justice and Administration, Republic of Slovenia, hereby declares that this document entirely corresponds to the original Slovene text.

Ljubljana, 8 June 2005

